PHARMACOTHERAPY REVIEW

CNS STIMULANTS
for treatment of
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

I. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), formerly called hyperkinesis or minimal brain dysfunction, is defined by its diagnostic features. ADHD is characterized by two distinct sets of symptoms, **inattention** and/or **hyperactivity/impulsivity**. Although these two sets of symptoms typically occur together, one may be present without the other. These symptoms are maladaptive and inconsistent with developmental level. The manifestations of inattention and hyperactivity/impulsivity are included in Appendix A (DSM-IV-TR Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder).[1] The diagnosis of ADHD requires the presence of at least six manifestations from the inattentiveness cluster of symptoms, six from the hyperactivity/impulsivity cluster, or both. Symptoms must be constant for at least six months and present in at least two distinct settings (e.g., home, school or work). Evidence confirming the ADHD diagnosis is often obtained directly from teachers as well as parents.

The component of **inattention** may become obviously apparent in the school environment as frequent failure to pay attention to details, easy distractibility, failure to finish tasks, avoidance of things requiring concentration and a sustained mental effort, careless mistakes, disorganization and/or poor follow-through on tasks. The **hyperactivity** component generally manifests itself before age seven.

While the behaviors of ADHD occur in virtually all children, the frequency in ADHD is very high. With improperly diagnosed and treated ADHD, symptoms can lead to poor academic performance, conflict with parents, teachers and peers, and low self-esteem. Inattention tends to persist into adulthood. Motor hyperactivity and impulsivity tend to decline with age.

II. INCIDENCE

ADHD is the most common chronic neurobehavioral disorder of childhood.[2] Reported rates vary in different geographical areas due to a number of factors, including inconsistent application of reliable diagnostic processes by different health care professional groups (e.g., primary care physician v. pediatrician v. neurologist v. psychiatrist). According to the National Institute of Mental Health, ADHD affects 3% to 5% of all school-age children (perhaps as many as 2.0 million U.S. children). The prevalence of ADHD is approximately 2 to 3 times higher in school-age boys than girls. The gender ratio in adolescents is closer to 1:1, and among young adults women experience ADHD twice as frequently as men. ADHD is not generally a condition that children "outgrow." ADHD persists into adolescence in 60% to 80% of children and into adulthood in about 66% of cases.[3-9]

III. ETIOLOGY

The etiology of ADHD is not known. Genetics, neurotransmitter deficits and perinatal complications have been implicated. The genetic and neurobiological etiologies appear to be the most plausible. ADHD has a heritability of 0.75 to 0.91.[10] Dysregulation of the neurotransmitter dopamine in pathways of the brain thought to play significant roles in ADHD (the dopamine hypothesis) has many followers. It postulates that ADHD is due, in large part, to inadequate dopamine in key areas of the brain. The effectiveness of CNS stimulant drugs in the management of ADHD supports the dopamine hypothesis as they (CNS stimulants) increase the release of dopamine and norepinephrine from presynaptic neurons in the central nervous system and inhibit their reuptake, thereby increasing the amount of these chemicals in neuronal synapses.

The following have been ruled out as likely causes or contributors to ADHD: head trauma, refined sugar intake, food allergies, artificial flavorings or preservatives, poor schools, poor parenting or too much TV. Abuse of alcohol, illegal drugs or cigarette smoking during pregnancy could interfere with brain development and contribute to the development of ADHD.

IV. TREATMENT

A. Goal of Therapy

The primary goal in treating ADHD is to produce the best possible therapeutic outcome for the patient, which translates into improved functional ability at school, at work, in the community and at home. This goal can be achieved in a high percentage of ADHD patients with drug therapy, psychosocial therapy or a combination of these approaches. Occasionally one or more additional behavioral disturbances will coexist with ADHD. These comorbidities must be managed specifically while concurrently managing ADHD. Psychiatric or behavioral disorders that underlie ADHD can confound the diagnosis of ADHD significantly.

B. Behavior Therapy

Behavior therapy is most often an adjunct to drug therapy in managing ADHD It is not a substitute for drug therapy because it is less effective than drug therapy in managing the core symptoms of ADHD. Behavior therapy seeks to improve behavior by altering the physical and social environment, setting specific goals, providing rewards for meeting goals and establishing consequences for failure to meet goals (i.e., positive and negative reinforcement).

C. Drug Therapy

Psychostimulant drugs have been the drug treatment of choice for children with ADHD since a report in 1937 revealed the value of racemic amphetamine in improving the conduct and academic performance of children with behavioral disturbances.[11] These findings over 65 years ago have been confirmed over and over in many controlled, short-term and long-term studies of children, adolescents and adults diagnosed with ADHD.[12-24]

The response rate to any single stimulant produces a dramatic and consistent improvement of core symptoms of inattention, hyperactivity and impulsivity in approximately 70% of children, adolescents and adults. Up to 90% of children will respond to at least one stimulant indicated for the treatment of ADHD without major adverse effect if drug titration is done carefully.[22]

D. CNS Stimulants Indicated to Treat ADHD

CNS STIMULANTS INDICATED TO TREAT ADHD					
Generic Name	**Brand Name**	**Generic Available**	**Strength (mg)**	**Dosage Form**	**Frequency Of Dose**
RAPID ONSET/SHORT DURATION PRODUCTS					
Amphetamine Mixture	Adderall	Yes	5, 7.5, 10, 12.5, 15, 20	Tab	1 – 2x/d
Dexmethylphenidate	Focalin	No	2.5, 5, 10	Tab	2x/d
Dextroamphetamine	Dexedrine; DextroStat	Yes	5, 10	Tab	1 – 2x/d
Methamphetamine	Desoxyn	No	5	Tab	1 – 2x/d
Methylphenidate	Ritalin, Methylin	Yes	5, 10, 20	Tab	1 – 2x/d
SLOWER ONSET/LONG DURATION					
Dextroamphetamine sulfate	Dexedrine Spansule	Yes	5, 10, 15	Cap (SR)	1x/d
Methylphenidate HCℓ	Metadate ER	No	10	TAB (ER)	1x/d
	Metadate ER	Yes	20	TAB (ER)	1x/d
	Methylin ER	No	10	TAB (ER)	1x/d
	Methylin ER	Yes	20	TAB (ER)	1x/d
	Ritalin SR	Yes	20	TAB (ER)	1x/d
Pemoline	Cylert	Yes	18.75, 37.5, 75	TAB	1x/d
	Cylert	No	37.5	Chew Tab	1x/d
RAPID ONSET/LONG DURATION					
Amphetamine Mixture	Adderall XR	No	5, 10, 15, 20, 25, 30	Cap (ER)	1x/d
Methylphenidate HCℓ	Metadate CD	No	20	Cap (ER)	1x/d
	Ritalin LA	No	20, 30, 40	Cap (ER)	1x/d
Methylphenidate HCℓ	Concerta	No	18, 27, 36, 54	TAB (ER)	1x/d

Note:

1. The mixture of amphetamines in Adderall and Adderall XR are equal amounts of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate and amphetamine sulfate.
2. Pemoline (Cylert) should be avoided, if possible, due to the risk of severe drug-induced hepatotoxicity.
3. Dexmethylphenidate (Focalin), the d- enantiomer of racemic d-, *l*-methylphenidate, is a short-acting agent. It has not shown clinical superiority in 3 small, short-term clinical trials over racemic methylphenidate. Patients who fail methylphenidate are unlikely to respond to dexmethylphenidate.[28]

E. Dosing of CNS Stimulants in Management of ADHD

The individual response to different doses of different stimulants in different delivery systems is highly variable. The best dose is the optimally effective dose that produces minimal adverse effects. The "start low, go slow" approach to stimulant dosing is strongly encouraged. Dosages should not be titrated upward more frequently than once weekly. Titration of doses upward in weekly increments allows adequate assessment of the effectiveness and tolerability of each dose. The first dose that produces a positive response may not be the optimal dose. Titration of doses over a 3 to 4 week period usually allows for a reliable assessment of the optimal dose. Dosages may need to be adjusted throughout treatment to maintain an optimal response.

Although daily dosing is the most common regimen, some physicians will utilize a 5-day (usually weekday) regimen if target symptoms occur primarily at school or in the work place. Because ADHD symptoms vary over time, stimulant therapy should be tapered and then stopped periodically (e.g., once a year) to determine whether continued stimulant therapy is medically necessary. When adjusting doses, patients should be monitored closely for adverse effects (e.g., insomnia of $\geq$ 1.0 to 1.5 hours, headache, aggression, feeling "bad").

Patients should be advised that therapeutic adherence is very important. If a particular stimulant fails to achieve therapeutic objectives or produces intolerable adverse effects, another stimulant should be tried.

As most dosage guidelines address children in the 6-12 year range, larger doses may be required as children with ADHD reach adolescence and adulthood.

Pemoline is not considered to be first or second-line therapy for the management of ADHD because of the risk of hepatotoxicity. One might consider pemoline use when three or more other stimulants have been tried without success.

F. Choice of Stimulant Preparations

The drugs of choice for patients with ADHD are methylphenidate and dextroamphetamine.[21] Methylphenidate is the most prescribed and studied stimulant in the management of ADHD.[21]

The efficacy of methylphenidate and dextroamphetamine are considered to be equal.[21] The side effect profile of the two drugs is also similar.

In one study of sustained release methylphenidate, sustained release dextroamphetamine and immediate release methylphenidate, the therapeutic effectiveness of all three preparations was similar.[25] Birmaher et al also found little difference between sustained-release and immediate-release methylphenidate.[26]

Selection of treatment choice is highly subjective. Products are now available as (1) rapid onset/short duration (conventional, immediate-release formulations), (2) slower-onset/longer-duration formulations and (3) rapid onset/longer duration products (see item D). Onset and duration of action of the different product groups are included below.

Product Group	Onset of Action (min)	Duration of Action (hrs)
Rapid Onset/Short Duration	20 – 30	3 – 6
Slower Onset/Longer Duration	30 – 60	4 – 8
Rapid Onset/Longer Duration	20 – 30	8 – 12

The choice of CNS stimulant product to treat ADHD is also determined by the drugs tolerability relative to adverse effects. Adverse effects to the CNS stimulants are similar in frequency, severity and duration.[26] The most common adverse effects to the stimulants are decreased appetite, stomachache, weight loss, insomnia, mood disturbances, headache, jitteriness, irritability, dry mouth, elevated blood pressure and dizziness. Transient motor or vocal tics may occur but usually subside over time or when the dosage is reduced. At oral doses utilized to treat ADHD, euphoria and psychological dependence is rare. Most side effects can be managed by lowering the dosage, but this could compromise quality of care. Most side effects are mild and will recede over time without significant dosage adjustment as the body regulates itself through various homeostatic processes.

G. Alternative ADHD Therapies

Although SSRI antidepressants have not been shown to be effective ADHD therapies, the tricyclic agents, imipramine and desipramine, and bupropion are considered second-line therapies for treating ADHD in patients unresponsive to stimulants.

Clonidine and guanfacine are less effective than stimulants in treating ADHD. Most clinicians are reluctant to use these products off-label to treat ADHD because of their adverse effects.

Atomoxetine is a nonstimulant drug indicated for ADHD. It is not a controlled substance and is indicated for use in adults as well as children. Atomoxetine is a selective norepinephrine reuptake inhibitor. The immediate, dramatic effect that stimulants produce has not been seen in children with ADHD treated with atomoxetine. Long-term safety and efficacy has not yet been adequately documented in well-controlled comparative trials.[27]

H. Controversies in Treating ADHD

Stimulant drug effectiveness in managing ADHD and improving the ability to focus, learn and work is well established, but controversy is associated with their use. The stimulant drugs are all in DEA Schedule II (high abuse and diversion potential) except for pemoline, which is in Schedule IV. There is, however, little evidence to suggest that stimulant abuse or diversion is a major problem among those being treated for ADHD.[26]

Issues of overdiagnosis of ADHD and inappropriate prescribing of psychostimulants persist. Most researchers are of the opinion that increased use of stimulants reflects better diagnosis and more effective treatment of ADHD from childhood into adulthood.

Whether CNS stimulants consumed chronically in children alters growth has been debated. Some studies suggest that stimulants may slow weight gain and growth slightly and temporarily, but long-term effects are either minimal or do not affect final adult height.[29-30]

V. RECOMMENDATIONS

Among the **rapid acting/short duration** products, generic versions of a 4 drug amphetamine/dextroamphetamine mixture, dextroamphetamine and methylphenidate exist that provide a full spectrum of doses for once or twice daily administration. No brand name **rapid acting/short duration** CNS stimulants are recommended for preferred drug status as they do not offer any significant or compelling clinical advantage relative to safety and/or effectiveness over their multisource versions.

Among the **slower onset/long duration** products, generic versions of dextroamphetamine sulfate and methylphenidate exist that provide a full spectrum of doses for once a day administration. Pemoline (Cylert) is also available in three strengths as a generic tablet formulation, but the use of this agent is strongly discouraged. No brand name **slower onset/long duration** CNS stimulants are recommended for preferred drug status as they do not offer any significant or compelling clinical advantage relative to safety and/or effectiveness over their multisource versions.

The **rapid onset/long duration** products offer no appreciable safety or effectiveness advantage over the **rapid onset/short duration** or **slower onset/long duration** products and there are no generic alternatives to these brand name products. There is little objective clinical evidence relative to safety and/or efficacy to support the contention that therapeutic adherence and clinical outcomes are significantly better with the use of the **rapid onset/long duration** products v. **slower onset/long duration** or even **rapid acting/short duration** formulations. It is recommended that no brand name **rapid onset/long duration** products be recommended for preferred drug status.

APPENDIX A

DSM-IV-TR DIAGNOSTIC CRITERIA FOR

Attention-Deficit/Hyperactivity Disorder

DIAGNOSTIC CRITERIA FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. Either (1) or (2)

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

- often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- often has difficulty sustaining attention in tasks or play activities
- often does not seem to listen when spoken to directly
- often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior[a] or failure to understand instructions)
- often has difficulty organizing tasks and activities
- often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- often fidgets with hands or feet or squirms in seat
- often leaves seat in classroom or in other situations in which remaining seated is expected
- often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- often has difficulty playing or engaging in leisure activities quietly
- is often "on the go" or often acts as if "driven by a motor"
- often talks excessively

Impulsivity

- often blurts out answers before questions have been completed
- often has difficulty awaiting turn
- often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

[a] Resisting work or school tasks that require self-application because of an unwillingness to conform to the demands of others is oppositional behavior.

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PHARMACOTHERAPY REVIEW

ANTIHYPERLIPIDEMIC THERAPIES

I. INTRODUCTION

Approximately 100 million Americans have total blood cholesterol levels of ≥ 200 mg/dL. Hyperlipidemic states are associated with atherosclerosis. Low-density lipoprotein cholesterol (LDL) elevation correlates directly with coronary heart disease (CHD), the single largest killer of men and women in the U.S. [1] Atherosclerotic vascular disease is responsible for approximately 75% of cardiovascular mortality. In 2002, approximately 1.1 million adults in the U.S. experienced new or recurrent myocardial infarction and 40% died.[1] Direct and indirect costs of CHD exceed $100 billion per year. [1]

II. PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Succinctly stated, atherosclerosis is a multifactorial vascular process involving proliferation of intimal smooth muscle cells with accumulation of macrophages and T lymphocytes, ↑ in connective tissue matrix, and ↑ of cholesterol esters and free cholesterol in smooth muscle and endothelial cells. [2] Vascular lesions form when cholesterol-rich lipoproteins are deposited in macrophages. This leads to foam-cell formation and eventually to atherosclerotic plaque. [2]

Once formed, plaque may be "stable" or "unstable." Plaque can rupture and produce a nonocclusive or occlusive thrombus with the consequence being angina, myocardial infarction or sudden death.

The main body lipids are cholesterol, triglycerides and phospholipids. They are transported through the bloodstream as complex molecules called lipoproteins. Cholesterol is classified by the lipoprotein in which it is carried. These are low-density lipoprotein (LDL) cholesterol, very- low-density-lipoprotein (VLDL) cholesterol, intermediate-density lipoprotein (IDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. The sum of these parts represents the total cholesterol measurement.

Most of the cholesterol in blood and atherosclerotic plaque is typically LDL-cholesterol and **high** plasma concentrations of LDL-cholesterol are associated with atherosclerotic cardiovascular disease.

Elevated triglycerides, carried primarily in VLDL, IDL and chylomicrons are also associated with increased cardiovascular risk. Apolipoproteins are protein constituents of lipoproteins and **high** concentrations of lipoprotein (a) and lipoprotein B (the major protein component of LDL, IDL and VLDL) have been associated with increased risk of coronary artery disease.

A **low** plasma concentration of protective high-density lipoprotein (HDL) cholesterol is a strong risk factor for coronary artery disease, even in the presence of normal levels of LDL and total cholesterol. High concentrations of apolipoprotein A1 are associated with high levels of HDL-cholesterol and lower coronary artery disease risk.

III. TREATMENT GUIDELINES

Clinical trials demonstrating cardiovascular risk reduction with lowered serum lipids led to the release of a new set of national cholesterol treatment guidelines in 2001.[3-18] In these new guidelines, the National Cholesterol Education Program (NCEP) – Adult Treatment Panel (ATP) III Guidelines, the role of LDL as the major atherogenic lipid component remained the primary focus, but non-HDL goals, as well as LDL goals, are addressed by NCEP – ATP III.[19]

NCEP-ATP III guidelines define an LDL below 100 mg/dL as optimal. An LDL below 100 mg/dL is the recommended goal for those who have experienced a CHD event (i.e., myocardial infarction stable and unstable angina, revascularization procedure). The NCEP-ATP III guidelines went further to define a primary prevention population who have not yet experienced a CHD event and define this category as CHD risk equivalent (see Table I). This population (CHD risk equivalents) has the same aggressive LDL-lowering goal as those with diagnosed CHD. CHD risk equivalents include patients with noncoronary atherosclerosis (symptomatic carotid artery disease, abdominal aortic aneurysm, peripheral arterial disease), diabetes and an ATP III Framingham-based CHD 10-year risk estimate > 20%.

Additional CHD treatment decision points and LDL goals, based on risk, are presented in Table 1.

Table 1. CHD Risk Status, LDL Goal and Treatment Decision Points[19]

Risk Status	LDL Goal	Level to Begin Lifestyle Change Therapies	Level to Consider Drug Therapy
CHD + CHD risk equivalents[a]	< 100 mg/dL	≥ 100 mg dL	≥ 100 mg/dL[b]
≥ 2 CHD risk factors[c]			
10-20% 10-yr risk	< 130 mg/dL	≥ 130 mg/dL	≥ 130 mg/dL
< 10% 10-yr risk	< 130 mg/dL	≥ 130 mg/dL	≥ 160 mg/dL
< 2 CHD risk factors[c]	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL

[a] Risk equivalents are noncoronary atherosclerosis, diabetes, greater than 20% 10-year CHD risk.
[b] If the LDL level is above 130 mg/dL, drugs may be started simultaneously with diet therapy. If the level is 100-130 mg/dL, drug therapy may be considered, especially if lifestyle changes do not achieve the goal.
[c] Risk factors are man over 45 years of age, woman over 55 years of age, family history of premature CHD, high blood pressure, HDL below 40 mg/dL, current cigarette smoking.

LDL-lowering strategies reduce CHD risk and CHD events by about 30% in 5 years (and perhaps more with longer courses of therapy). The remaining 70% of patients still experience a CHD event. The need for further risk reduction is obvious.

A high triglyceride level may be a risk factor one can target as evidence indicates elevations in triglyceride levels, as well as LDL levels, amplify CHD risk.[20-21] An elevated triglyceride level probably does not contribute to atherogenesis per se, but probably does signal the presence of a variety of lipid abnormalities (e.g., ↑ VLDL, IDL, ↓ HDL, ↑ levels of small, dense LDL). Patients with high triglyceride (and LDL-cholesterol) levels often have several other CHD risk factors (e.g., central obesity, impaired glucose tolerance, hypertension). This complex set of findings has been known as syndrome X, Reavan's syndrome, dysmetabolic syndrome and most recently as metabolic syndrome by NCEP-ATP III.

To enhance the potential for CHD risk reduction, NCEP-ATP III produced two major recommendations in addition to treatment decision points to lower LDL-cholesterol levels to goal (Table 1).

First, NCEP-ATP III guides identification of patients with metabolic syndrome and recommends therapeutic lifestyle changes focusing on weight reduction and exercise, utilization of drugs to lower triglycerides and raise HDL, reduce thrombogenic potential with daily aspirin use, and treat hypertension effectively. [21]

Second, NCEP-ATP III recommends that secondary treatment targets, defined by non-HDL (total cholesterol minus HDL) be established for patients who have triglyceride levels > 200 mg/dL after LDL goals have been achieved. (see Table 2). [21] Time and additional clinical trials will document the value of meeting non-HDL goals.

Table 2. LDL and Non-HDL Goals for Patients with Triglyceride Levels > 200 mg/dL[19]

Risk Status	LDL Primary Goal	Non-HDL Secondary Goal
CHD or risk equivalent[a]	< 100 mg/dL	< 130 mg/dL
≥ 2 risk factors[b]	< 130 mg/dL	< 160 mg/dL
< 2 risk factors[b]	< 160 mg/dL	< 190 mg/dL

[a] Risk equivalents are diabetes, metabolic syndrome, greater than 20% 10-year CHD risk.
[b] Risk factors are man over 45 years of age, woman over 55 years of age, family history of premature CHD, high blood pressure, HDL below 40 mg/dL, current cigarette smoking.

IV. TREATMENT CHALLENGES

The NCEP-ATP III guidelines increased the number of patients who are appropriate candidates for LDL-lowering from approximately 13 million to approximately 32 million. Of these, approximately 20 million would be candidates for an LDL goal of 100 mg/dL or less. Before NCEP-ATP III, it was estimated that only about 18% with an LDL-cholesterol **goal** of ≤ 100 mg/dL reached their goal. [22, 23] Further, how to best achieve non-HDL goals is very challenging.

LDL TREAMENT GOALS

"Statins" have been and remain the drugs of first choice to lower LDL-cholesterol. LDL-cholesterol lowering may also provide risk reduction by stabilizing plaque, reducing inflammation and restoring endothelial function.

Dose-related reduction in LDL-cholesterol, according to manufacturer prescribing information, is included in Table 3. [24] The impact of selected doses of statins on HDL and triglycerides is included in Table 4. [24]

Table 3. Typical Dose-Related Reduction of LDL with Statins

Drug	Daily Dose (mg)	% Reduction
Atorvastatin	10	39
	20	43
	40	50
	80	60
Fluvastatin	20	22
	40	25
	80	36
Lovastatin	20	27
	40	32
	80	42
Pravastatin	10	22
	20	32
	40	34
Simvastatin	5	26
	10	30
	20	38
	40	41
	80	47

Data derived from manufacturer prescribing information (Lipitor/Pfizer, Lescol/Novartis, Mevacor/Merck, Zocor/Merck and Pravachol/Bristol-Myers Squibb).

Table 4 Impact of Selected Statin Doses on HDL and Triglycerides

Drug	Dosage	↑ HDL (%)	↓ TG (%)
Atorvastatin	80 mg/day	6	29
Fluvastatin	40 mg/day	8	10
Lovastatin	80 mg/day	8.6	16
Pravastatin	40 mg/day	12	24
Simvastatin	80 mg/day	12	18

Data derived from manufacturer prescribing information (Lipitor/Pfizer, Lescol/Novartis, Mevacor/Merck, Zocor/Merck and Pravachol/Bristol-Myers Squibb).

Most patients with CHD require only a 30% LDL reduction to achieve their NCEP-ATP III goal.[24] This is attainable with mid-range doses of most statins. Relatively few patients require LDL reduction of 40% to 60% to achieve their NCEP-ATP III goal.

Statins decrease cholesterol synthesis by the liver by inhibiting the hepatic enzyme HMG-CoA reductase. The net effect is lowering of cholesterol-carrying lipoproteins, the most significant being LDL.

Several large scale, randomized clinical trials provide convincing evidence that statins are effective in reducing CHD events in both primary and secondary prevention. Much of the evidence relates to lovastatin, pravastatin and simvastatin (see Table 5 and Appendix A).

Table 5. Summary of Selected Clinical Trials Documenting Primary and Secondary Prevention of CHD[19, 24]

Study	No. of Patients	Follow-up (yrs)	Drug	LDL/HDL Change (%)	Total Mortality (%)	CHD Death Nonfatal MI (%)	PTCA, Bypass (%)
Primary prevention							
LRC-CPPT[3]	3806	7.4	BAS	-13/2	-7	-19	NR
AFCAPS/TexCAPS[13]	6605	4.8	Lovastatin	-25/6	NR	-40	-33
WOSCOPS[12]	6595	4.9	Pravastatin	-26/5	-22	-31	-37
HHS[7]	4081	5	Gemfibrozil	-10/10	0	-34	NR
Secondary prevention							
CDP[6]	1119	15	Niacin	-10/NA	-11	NR	NR
4S[11]	4444	5.4	Simvastatin	-35/8	-30	-34	-34
CARE[10]	4159	5	Pravastatin	-28/2	-9	-24	-27
LIPID[9]	9014	6	Pravastatin	-25/6	-22	-24	-20
PostCABG[15]	1351	4.3 + 3[a]	Lovastatin	-40/4	-35	-31	-30
VA-HIT[8]	2531	5.1	Gemfibrozil	0/6	-11	-22	-9
BIP[4]	3090	6.2	Bezafibrate	-7/18	+6	-11	-4
POSCH[5]	838	14.7	Surgery	-38/4	-25	-40	-69

LRC-CPPT = Lipid Research Clinics–Coronary Primary Prevention Trial; BAS = bile acid sequestrant; NR = not reported; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study; HHS = Helsinki Heart Events; CDP = Coronary Drug Project; NA = not applicable; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; BIP = Bezafibrate Infarction Prevention Study; POSCH = Program on the Surgical Control of Hyperlipidemias.

[a] Original study was 4.3 years; follow-up analysis was 3 years.

Some argue that the beneficial effects of statins are a class effect, and that may be true, but the preponderance of the evidence, regardless of relative LDL-lowering "potency" supports the use of lovastatin, pravastatin and simvastatin (see Table V and Appendix A).

Benefits of improved quality of life and lengthened life are well documented with lovastatin, pravastatin and simvastatin. CHD and cardiovascular events associated with atherosclerosis, including episodes of unstable angina, strokes, revascularization procedures including percutaneous coronary angiography and coronary artery bypass, fatal and nonfatal myocardial infarction and sudden CHD death are reduced about 33% with 5 years of statin treatment. The Heart Protection Study, which evaluated over 20,000 patients with CHD or a CHD risk equivalent found that patients with CHD, PVD, stroke-TIA, or DM experienced a 24% reduction in risk of vascular events after 5 years of treatment with 40 mg/day of simvastatin. This benefit was seen in all age groups, in both men and women and in patients with all levels of baseline LDL.

Statins are safe and well tolerated. They are rarely discontinued because of adverse effects. The most common adverse effects are mild g.i. complaints, fatigue, headache or myalgias. Elevation in hepatic serum aminotransferase levels $\geq$ 3x the upper limit of normal on 2 consecutive occasions (high liver function test results) occurs in less than 1% of patients taking starting doses of statins and up to 2.5% of those taking the highest daily dosage available.[24] These elevations are usually transient and self-limiting. Discontinuation of therapy is rarely necessary.

Muscle toxicity is the most serious potential adverse effect. Muscle weakness, tenderness or pain with creatine kinase (CK) levels >10x the upper limit of normal is rare, occurring in approximately 2 - 4 patients/1000 treated. Rhabdomyolysis may occur in 10 – 20 patients per 1,000,000 treated.[24] Risk of myopathy increases in the presence of compromised renal function, the elderly, or in patients taking drugs that interfere with statin metabolism.[19]

In 5 major trials and over 77,000 patient-years of statin exposure, 8 cases of myopathy were reported.[9-13] The MRC/BHF Heart Protection Study detected myopathy in 9 of 10,269 patients treated with simvastatin for 5 years.[24] Risk of myopathy among currently marketed statins is very low.

Alternatives to statins are available if statins are not well tolerated or are contraindicated. Logical alternatives are bile acid sequestrants (BAS) or a niacin formulation to lower LDL. BASs lower LDL 15% to 25%, are very safe, and have been shown to reduce CHD events (see LRC-CPPT study, Table 5). The disadvantages of BASs are taste, consistency and their propensity to produce constipation, bloating, abdominal pain and gas. Colesevelam, a newer BAS, is available in tablet form and produces fewer side effects than powders and granules.

Niacin is used more and more in lipid management and has been shown to reduce CHD events.[24] It is the most effective agent for raising HDL and also effectively lowers triglycerides as well as LDL. Flushing and itching are bothersome side effects but can be minimized or avoided by premedication 30 minutes before a niacin dose with 325 mg aspirin or 200 mg of ibuprofen. Up to 70% of patients tolerate niacin on a long-term basis. Extended-release niacin allows a once daily bedtime dose. Niacin-induced hepatotoxicity has occurred when doses exceed 1.5 g/day.

Combination therapy involving niacin and/or a BAS, with or without a statin, may be indicated. The combination of niacin and a BAS can lower LDL as much as 50%. When a statin alone is not enough to reach the LDL goal, a BAS, niacin, or both may be added to the statin regimen. When combined, the lower LDL achieved is generally the sum of the lowering provided by each drug (i.e., an additive effect). The addition of a BAS or niacin to statin therapy lowers LDL more than would a doubling of the statin dose.[25, 26] A triple drug regimen of lovastatin, niacin and colestipol produced a 60% LDL lowering. In this study, 83% of patients achieved their LDL goal of < 100 mg/dL.[27] Combination therapies should not be discounted. The additive effect can be significant and when combined, lipid lowering agents may be taken in lower, more tolerable and potentially safer doses.

NON-HDL TREATMENT GOALS

Non-HDL (i.e. total cholesterol minus HDL) treatment goals and guidelines are identified by NCEP-ATP III (see Table 2). Statins lower non-HDL as well as LDL. Thus, patients who have elevated LDL and triglycerides (indicating increased levels of triglyceride-laden VLDL and IDL remnants) and high liver secretion of VLDL particles from the liver can benefit significantly from statin therapy. Statin non-HDL lowering parallels their LDL lowering capacity and appears to be dose-related.[28] Statins are most effective when the non-HDL level is within 30 mg/dL of the goal. Non-HDL levels above this will probably require combination therapy with a statin and a triglyceride lowering drug (i.e., niacin, a fibrate, fish oils).

Fibric acid lowering agents modestly increase LDL lowering of the statins, and the significant triglyceride lowering effects of the fibric acid derivatives are modestly enhanced by the statins. The increase in HDL with the statin/fibric acid combination appear to be additive.

Niacin administered with a statin lowers triglycerides and raises HDL effectively while also lowering LDL. These effects appear additive. In one study, LDL was reduced an additional 8% and 24% when 1.0 g and 2.0 g daily doses of extended release niacin were added to a statin regimen.[29] Fish oils can lower triglycerides 30% to 40% but have little effect on HDL and may actually raise LDL slightly. The omega-3 fatty acids may have other positive effects (e.g., reduction of fibrinogen levels, reduction of blood pressure and cell proliferation).[30] Omega-3 fatty acids are associated with significant CHD risk reduction when incorporated into the diet or taken as dietary supplements.[31, 32] Fish oils significantly enhance the triglyceride lowering properties of statins, primarily by reducing VLDL and IDL concentrations.[33]

Fibric acid derivatives appear to be tolerated better than immediate release niacin. In the diabetic patient, fibric acid derivatives are less likely than niacin to alter glucose tolerance.

A major issue in combining a fibric acid derivative with a statin is the risk of myotoxicity that is reversible upon drug discontinuation. The risk of myositis, with or without a statin, appears higher with gemfibrozil than fenofibrate. The risk of myositis and rhabdomyolysis with currently available statins and gemfibrozil (0.2% to 0.4%) is not as great as that seen when cerivastatin was given in combination with gemfibrozil (~5%).

Suggestions for achieving LDL and non-HDL goals in patients with mixed hyperlipidemia are included below:[24]

- Try to achieve LDL and non-HDL goals with a statin alone.
- If the addition of a triglyceride-lowering drug to the statin is required, give preference to niacin or fish oils, as the risk of myopathy appears low. If a fibrate is to be added, fenofibrate is preferred over gemfibrozil since it may have a lower risk of myopathy.
- Prescribe the lowest effective dosages of the statin and fibrate to achieve treatment goals (starting dosage of statin with fenofibrate, 67-134 mg/day).
- Dose the fibrate in the morning and the statin in the evening (this suggestion is based on theoretical considerations and not on evidence that it will reduce the frequency of muscle toxicity).
- Avoid (or prescribe cautiously) statins in patients who have compromised renal or hepatic function.
- Ensure that no other drugs are or will be taken concurrently that could interfere with the metabolism of the statin.
- Obtain a baseline CK level and repeat the measurement during therapy if the patient reports muscle symptoms.
- Teach patients to recognize and report muscle weakness, tenderness, or pain, and be prepared to evaluate those who experience these symptoms.
- Discontinue therapy if muscle symptoms are present and CK is more than 10 times the upper limit of normal.

V. OTHER LIPID-LOWERING THERAPIES

A so called “super statin,” rosuvastatin (Crestor) was approved by the FDA in August, 2003. The approval was delayed because of adverse effects associated with an 80 mg dose. The 5, 10, 20 and 40 mg strengths were approved. Rosuvastatin, like other statins, reduces LDL and triglycerides in a dose dependent manner. Rosuvastatin will not be eligible for P&T Committee review until it has been on the market in general use for a minimum of 6 months.

Another drug, relatively new to the market, is ezitimibe (Zetia). This drug has a unique mechanism of action. It works through a local effect in the g.i. tract to inhibit exogenous cholesterol absorption. Ezitimibe only lowers serum LDL levels approximately 18% when taken alone or in combination with a statin.[34] Its effects on HDL and triglycerides are modest. Its primary niche is as a well tolerated adjunct to statins in patients requiring significant LDL-lowering. Its primary or adjunctive role in managing mixed dyslipidemias requiring elevated HDL levels and/or lowered triglyceride (non-HDL lipid lowering) is minimal.

VI. PRODUCT INFORMATION

Products considered in this review are included in Table 6 below:

Table 6. Agents Indicated to Treat Hyperlipidemias

Generic Name	Brand Name	Generic Available	Strength (mg)	Dosage Form	Freq of Dose
HMG-CoA Reductase Inhibitors ("Statins")					
Lovastatin	Mevacor	Yes	10, 20, 40	TAB	1/day
Lovastatin	Altocor	No	10, 20, 40, 60	TAB (ER)	
Simvastatin	Zocor		5, 10, 20, 40, 80	TAB	
Pravastatin	Pravachol		10, 20, 40, 80	TAB	
Fluvastatin	Lescol		20, 40	TAB	
Fluvastatin	Lescol XL		80	TAB (ER)	
Atorvastatin	Lipitor		10, 20, 40, 80	TAB	
HMG-CoA Reductase Inhibitor ('statins") Combinations					
Pravastatin/ASA	Pravigard-PAC	No	20/81, 40/81, 80/81, 20/325, 40/325, 80/325	TAB	1/day
Bile Acid Sequestrants					
Cholestyramine	Questran, Questran Light, Prevalite	Yes	4 g	POW	1-2/day
Colestipol	Colestid	No	1 g	TAB	1-2/day
			5 g (granules)	GRAN	
			5 g/ 7.5 g	POW	
Colesevelam	Welchol	No	625	TAB	2/day
Fibric Acid Derivatives					
Gemfibrozil	Lopid	Yes	600	TAB	2/day
Fenofibrate	Tricor	No	54, 160	TAB	1/day
Fenofibrate	Lofibra	Yes	67,134, 200	CAP	1/day

Table 6. (Continued) Agents Indicated to Treat Hyperlipidemias					
Niacin and Niacin Combinations					
Niacin (Nicotinic Acid)	---	Yes	100, 250, 500	TAB	2/day
Niacin (Nicotinic Acid)	Niacor	Yes	500	TAB	2-3/day
Niacin (Nicotinic Acid)	Niaspan	Yes	500, 750, 1000	TAB (ER)	1/day
Niacin (Nicotinic acid)	---	Yes	125, 250, 400, 500	CAP (ER)	1/day
Niacin (ER)/ Lovastatin	Advicor	No	500/20, 750/20, 1000/20	CAP (ER)	1/day
Miscellaneous Agents (Cholesterol Absorption Inhibitor)					
Ezetimibe	Zetia	No	10 mg	TAB	1/day

VII. DRUG INTERACTIONS

Many drugs utilized to treat dyslipidemias interact adversely with a variety of other drugs in a clinically significant manner. The table below lists the most significant drug interactions with the antihyperlipidemic drugs relative to clinical severity.

Bile Acid Sequestrants
Anticoagulants (2)
Corticosteroids (2)
Digoxin (2)
Furosemide (2)
Levothyroxine (2)
Statins (2)
Valproic Acid (2)

Fibric Acid Derivatives
Anticoagulants (1)
Statins (1)

Niacin
No significance level (1) or (2) drug interactions

Statins

Atorvastatin (CYP3A4 metabolism)
Azithromycin (1)
Azole antifungals (1)
Bile Acid Sequestrants (2)
Clarithromycin (1)
Clopidogrel (2)
Cyclosporine (1)
Diltiazem (2)
Erythromycin (1)
Gemfibrozil (1)

Statins (continued)
Grapefruit juice (2)
Rifamycins (2)
Verapamil (2)

Fluvastatin (CYP2C9 metabolism)
Anticoagulants (2)
Bile Acid Sequestrants (2)
Gemfibrozil (1)
Rifamycins (2)

Lovastatin (CYP3A4 metabolism)
Antiarrhythmics (1)
Anticoagulants (2)
Azithromycin (1)
Azole Antifungals (2)
Bile Acid Sequestrants (2)
Clarithromycin (1)
Cyclosporine (1)
Diltiazem (2)
Disopyramide (1)
Erythromycin (1)
Gemfibrozil (1)
Grapefruit juice (2)
Rifamycins (2)
Verapamil (2)

Pravastatin (Sulfation)
Azole antifungals (2)
Bile Acid Sequestrants (2)
Cyclosporine (1)
Gemfibrozil (1)

Simvastatin (CYP 3A4 metabolism)
See lovastatin

VIII. ADVERSE EFFECTS

The most prevalent adverse effects from the various antihyperlipidemic therapies have been reported previously in this review. Less frequently occurring adverse effects are reported in package labeling.

IX. SUMMARY/CONCLUSION

NCEP-ATP III guidelines address non-HDL as well as LDL treatment goals. Therefore, the proper place of bile acid sequestrants, fibric acid derivatives (fibrates), niacin and miscellaneous lipid lowering drugs and combinations of lipid lowering drugs should be considered for use along with the statins.

It is estimated that only about 18% of hyperlipidemic patients in the general population who have an LDL goal of ≤ 100 mg/dL reach their LDL goal with drug therapy. When one considers the GOALLS study, and the fact that U.S. (≤ 100 mg/dL) and European (≤ 115 mg/dL) LDL goals were met in 72% to 93% of patients with a 20 mg dose of simvastatin, one can challenge the relative value of high potency statins and "super" statins. Perhaps factors such as therapeutic adherence/nonadherence, diet and lifestyle modification are not being addressed adequately by health care providers and patients in the management of hyperlipidemias.

It has been documented that most hyperlipidemic patients can reach their NCEP-ATP III LDL goal (see Table 1) with midrange doses of most statins when therapeutic adherence is good. Scientific evidence strongly supports lovastatin, pravastatin and simvastatin in primary and secondary prevention of CHD (see Table 5 and Appendix A).

Combination lipid lowering therapies should not be discounted or undervalued. Combination therapies can produce significant additive effects and will allow lower, more tolerable, and potentially safer doses of individual lipid lowering drugs. For example, niacin is being used more and more in lipid management to augment LDL and triglyceride lowering by statins and also raise HDL levels. Niacin added to a statin regimen can lower LDL more than doubling the statin dose.

Non-HDL, as well as LDL treatment goals (see Table 2), can be met by statins alone in many cases. Statins with the most effective triglyceride lowering potential are included in Table 4. When statins alone will not reduce triglycerides sufficiently, niacin or a fibrate can be added to the statin regimen. However, fibric acid derivatives only produce a modest LDL lowering along with a significant triglyceride lowering. Fish oils as nutritional supplements can lower triglyceride levels, but have little effect on HDL and may actually raise LDL slightly. Niacin, as previously stated, significantly enhances LDL and triglyceride lowering when combined with a statin and also raises HDL. Statins with the greatest potential to raise HDL most effectively, using equivalent does, are pravastatin and simvastatin (see Table 4).

When combined with a statin, the risk of myopathy is lower with niacin than with a fibrate.

Bile acid sequestrants lower LDL effectively, have been shown to reduce CHD events, are very safe, but are not particularly popular because of bloating, gas, abdominal pain, constipation and lack of palatability (powder and granules).

The only currently marketed cholesterol absorption inhibitor, ezitimibe, lowers LDL levels approximately 18%. When taken alone or in combination with a statin, however, its potential to lower triglycerides or elevate HDL is minimal.

Pravastatin and niacin have the lowest potential to interact adversely with other drugs. Pravastatin is the logical statin choice when patients are receiving other drugs (e.g., clopidogrel, azole antifungals, macrolide antibiotics, cyclosporine, rifamycins) metabolized by CYP3A4.

X. RECOMMENDATIONS

Given the need for an array of lipid-lowering drugs to meet NCEP-ATP III LDL-lowering and non-HDL lowering goals, guidance provided by NCEP-ATP III guidelines, and clinical evidence provided by primary and secondary prevention trials and other clinical trials, it is recommended to the P&T

Committee that all strengths of the following single-entity brand name drugs be granted preferred drug status:

pravastatin (Pravachol)
simvastatin (Zocor)

No brand name bile acid sequestrants, immediate or extended or controlled-release niacin or niacin combinations, immediate or extended release statin combinations, cholesterol absorption inhibitors or single-entity immediate or controlled-release statins, other than single-entity brand name pravastatin and simvastatin, are recommended for preferred drug status at this time because of the lack of compelling evidence of significant clinical advantage relative to safety and/or efficacy. Multisource versions of cholestyramine and immediate and extended-release niacin are available to complement statin therapy or to be used in the rare instance when a statin may not be tolerated. No brand name bile acid sequestrant or brand name immediate or extended-release niacin product offers any significant or compelling clinical advantage relative to safety and/or efficacy over multisource versions of bile acid sequestrant or immediate or extended-release niacin.

Because of a procedural matter, no recommendation(s) regarding the fibric acid derivatives (e.g., gemfibrozil, fenofibrate) will be made at the September 17, 2003 meeting. The fibric acid derivatives will be addressed at the December, 2003 P&T Committee meeting.

APPENDIX A

Summary of Selected Clinical Trials Documenting the Effectiveness and Safety of Selected Statins in CVD Risk Reduction

Primary Prevention
AFCAPS/TexCAPS (lovastatin)
WOSCOPS (pravastatin)

Secondary Prevention
4S (simvastatin)
LIPID (pravastatin)
CARE (pravastatin)
MIRACL (atorvastatin)

Safety/Other
PPP (pravastatin)
EXCEL (lovastatin)
MRC/BHF (simvastatin)
GOALLS (simvastatin)

AFCAPS/TexCAPS

(The Air Force/ Texas Coronary Atherosclerosis Prevention Study)

- Randomized, Double-blind, primary prevention, 6605 pts
- Treatment with lovastatin 20-40 mg/day resulted in 25% reduction in LDL, 6% HDL increase, 37% reduction in risk of first acute major coronary event.
- Persons with average TC and LDL levels and below average HDL may obtain significant clinical benefit from primary prevention lipid modification. On-treatment apoB, when combined with apoAI to form the apoB/AI ratio, may be a more accurate predictor than LDL of risk of first coronary event.
- Triglycerides reduced by 15 %, ApoB reduced by 18.9%, Apo B/AI reduced by 23.9%
- Participants in the highest tertile for the ApoB/AI ratio appeared to be at the greatest risk for an event.
- Lipid modification with lovastatin abolishes the excess risk for CHD associated with having a low HDL level at baseline.
- There is no evidence from this trial to support a threshold of benefit below which LDL reduction is not of clinical benefit.
- Although on-treatment LDL failed to predict risk in this trial, on-treatment ApoB and the ratio of apoB/AI proved to be significant primary predictors of coronary risk.
- The Quebec Cardiovascular Study documented that apoB is a more powerful independent predictor of CHD than LDL.
- These result suggest that reconsideration be given to apoB and AI in risk assessment and that treatment goals based on apoB or the apoB/AI ratio be further explored in certain populations

WOSCOPS

(West of Scotland Coronary Prevention Study)

- Randomized, primary prevention, men only
- Pravastatin 40 mg/day
- Examines the extent to which differences in LDL and other plasma lipids both at baseline and on treatment influence CHD risk reduction.
- Treatment effect of 40 mg/day of pravastatin is proportionally the same regardless of baseline lipid phenotype. There is no CHD risk reduction unless LDL levels are reduced, but a fall in the range of 24% is sufficient to produce the full benefit in patients taking this dose of pravastatin.
- LDL reduction alone does not appear to account entirely for the benefits of pravastatin therapy.
- Effects on HDL and VLDL are modest, but Apo B, VLDL remnants and IDL may be influenced by therapy.
- 6595 patients observing baseline HDL, LDL, and Triglycerides
- The percentage fall in LDL during treatment varied even in patients who complied with the treatment regimen. When the pravastatin group was divided the percent reduction observed a mean change from 0% to 39% reduction in LDL.
- Patients with no LDL reduction had RR similar to placebo but those with LDL reduction had risk reductions.
- Pravastatin reduced triglycerides by 12%, HDL increased by 7%, but neither was associated with change in risk.
- Pravastatin reduced total cholesterol and reduced risk of Coronary event. Observed risk reduction was 35%.
- They hypothesized that larger reductions in LDL would be associated with greater benefit, but no clear graded relationship was observed between LDL fall and risk reduction.
- The full benefit of about 45% risk reduction was seen in subjects who had mean reduction in the range of 24%, further decreases were not associated with larger risk reduction.
- Pravastatin removes triglycerides rich remnant particles from the bloodstream. These lipoprotein species have been linked to the progression of atherosclerotic lesion and their clearance may lead to stabilization of plaque whose rupture could give rise to clinical events.

4S

(Scandinavian Simvastatin Survival Study)

- Randomized, double-blind, 4444 patients (827 were women), simvastatin 20mg/day vs. placebo; patients have cholesterol in the range of 213-309
- This trail was to evaluate the morbidity and mortality in patients with CHD. These patients had previous MI, angina, and elevated serum cholesterol levels.
- The primary end point was death. 256 pts in the placebo group died and 182 patients in the simvastatin group died. 189 coronary deaths in the placebo group and 111 in the simvaststin group. 52 women died 25 in the placebo group and 27 in the simvastatin group.
- The secondary end point was major coronary events (nonfatal MI, coronary death, silent MI, or resuscitated cardiac arrest.) probably MI. 622 patients in the placebo group and 431 in the simvastatin group. 150 women had secondary end points. (91 in the placebo group and 59 in the simvastatin group)
- Simvastatin lowered total cholesterol by 25%, and LDL by 35%, increased HDL by 8%, reduced triglycerides by 10%.
- This study showed that long-term treatment with simvastatin is safe and improves survival in CHD patients.
- Dosages were adjusted by a computer program. Some patients were increased to 40 mg/day (37% of the patients) and other patients were decreased to 10 mg/day (2 patients)
- After 1 year 72% of the simvastatin patients had achieved the total cholesterol goal.
- One case of rhabdomyolysis occurred in a woman taking simvastatin 20mg/day and resolved when treatment was stopped.
- They indicate that adding simvastatin 20-40mg/day to treatment regimens in 100CHD patients would preserve life in 4 of 9 patients that would die from CHD, 7of 21 patients that would had nonfatal MI, and avoidance of revascularization in 6 of 19 anticipated patients.
- The impact of simvastatin on CHD seems to begin after about 1 year of therapy and increase steadily thereafter.
- Fewer new lesions and total occlusions developed in the simvastatin group. Coronary lesions may stabilize as there lipid core shrinks or at least does not further enlarge; there is a drop in risk of plaque rupture and thus may be the main reason for the improved survival rate observed in this trial.
- This trial is consistent with the idea that raised LDL cholesterol is and important factor in the pathogenesis of CHD.

LIPID

(The Long-Term Intervention with Pravastatin in Ischaemic Disease)

- Randomized, double-blind, 9014 patients (with history of MI or hospitalization for unstable angina and total cholesterol of 155 to 271, pravastatin 40 mg/day was used.
- The primary outcome was death. Death from CHD occurred in 6.4% of patients in the pravastatin group (a 24% relative reduction in risk) and 8.3% in the placebo group.
- The pravastatin group had a reduced risk of death by CVD (7.3% vs. 9.6% in the placebo group), CHD, MI (12.3% vs. 15.9%), stroke (3.7% vs. 4.5%), or death by any other cause (11.0% vs. 14.1%).
- Patients with total cholesterol <213- $\geq$ 251 had a risk reduction from 19-27%
- There were 8 cases of myopathy in the placebo group vs. 10 cases in the pravastatin group.
- Over the 6.1 years, we estimated that 30 deaths, 28 nonfatal MI, and 9 strokes were avoided in 48 patients for every 1000 randomly assigned to treatment with pravastatin, and 82 hospital admissions for unstable angina were also avoided.
- They found no evidence of a greater relative effect of treatment in women than in men.
- Treatment was safe and well tolerated.
- Treatment with pravastatin decreased mortality and should be considered for virtually all patients presenting with CHD.

CARE

(The Cholesterol and Recurrent Events Trial)

- Double-blind trial, 4159 patients (3583 men and 576 women), Pravastatin 40mg/day
- The patients had history of MI with cholesterol less than 240, and LDL levels averaging 115 to 174.
- The primary end point was fatal coronary event or nonfatal MI, the frequency of the end point was 10.2% in the pravastatin group and 13.2% in the placebo group, with yielded a 24% risk reduction.
- The frequency of stroke was reduced by 31%. The incidence of stroke was 3.8% in the placebo group and 2.6 in the pravastatin group.
- Pravastatin lowered the rate of coronary events more among women than men.
- The reduction in coronary events was also greater in patients with higher pretreatment levels of LDL.
- These results show that the benefit of cholesterol lowering therapy extends to the majority of patients with coronary disease who have average cholesterol levels.
- Patients with LDL greater than 175 had dietary counseling, and if the LDL stayed above 175, cholestyramine was prescribed in daily doses of 8 to16grams.
- Pravastatin lowered the mean LDL cholesterol by 32% and these levels were maintained throughout the 5-year follow-up.
- The higher the LDL the greater the risk reduction found when using pravastatin
- There were 45 deaths due to cancer in the placebo group and 49 in the pravastatin group.
- Breast cancer occurred in 1 patient in the placebo group and 12 in the pravastatin group. The patient in the placebo group had history of breast cancer, and 3 of the 12 had history of breast CA.
- Overall in the general population in treating 1000 of such patients, 150 cardiovascular events could be prevented, 51 patients would be spared from having one event. If the 1000 patients were at higher risk or women then the benefit would be greater.

MIRACL

(Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study)

- Randomized, double-blind 3086 patients, atorvastatin 80mg/day initiated 24-96 hours after an acute coronary syndrome (can this reduce the occurrence of early, recurrent ischemic events and death.)
- Primary end point (death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia) 228 patients in the atorvastatin group suffered an event and 269 in the placebo group.
- In conjunction with lowering LDL cholesterol, statins may improve endothelial function, decrease platelet aggregation and thrombus deposits and reduce vascular inflammation.
- At week 6 of the 16 weeks of study cholesterol goals had been met in the atorvastatin group. LDL was reduced 40%, Triglycerides reduced 16%, no major change in HDL in either group.
- There was no significant difference in risk of death, nonfatal MI, or cardiac arrest with resuscitation between the two groups, although the atorvastatin group had a lower risk of recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization.
- Moreover, among the atorvastatin-treated patients, there was no significant association between the percent change in LDL cholesterol from baseline to end of the study and the occurrence of a primary end point event.
- Nonetheless, the observation suggests that the decision to initiate intensive lipid-lowering therapy after ACS should not necessarily be influenced by serum lipid levels at the time of the event.
- 9 patients in the atorvastatin group suffered nonfatal stroke and 22 patients in the placebo group.
- Abnormal transaminase levels (>3 times ULN) occurred in 38 patients in the atorvastatin group and 9 in the placebo group.
- There were no cases of myositis.
- There was a 2.6% absolute reduction and 16% relative reduction in primary end point events.

PPP

(Prospective Pravastatin Pooling Project)

- Safety and tolerability are just as important as efficacy in determining clinical threshold to initiate long-term drug therapy to modify a risk factor.
- 40mg/day Pravastatin, double blind, randomized
- Statins decrease risk in patients with or without history of heart disease.
- WOSCOPS, CARE, LIPIDs formed the PPP to combine the experience of the 3 large CCT of single dose pravastatin.
- Statins inhibit a major hepatic enzyme so safety is an ongoing concern.
- The objective was to pool data to derive more precise estimates of the effectiveness of pravastatin in predefined subgroups, for less common events such as stroke, evaluate potential safety issues.
- Monitoring ALT and CPK at baseline and at 3, 6, 9, and 12 months
- Fewer pravastatin patients died over the five years that most patients were exposed to the drug (394 of 9809 vs. 502 of 9783 with placebo)
- There is a higher occurrence of breast CA in the pravastatin group compared to the placebo group. This was also noted in the CARE trial
- There was no difference in the serious adverse events related to the hepatobiliary system in the pravastatin group vs. the placebo group. (Most common was gallbladder disorders)
- No cases of myopathy. Patients that discontinued the medications for any reason were (2217 of 9809 vs. 2728 of 9783 in the placebo group).
- Concerns about myopathy and hepatic liver enzyme abnormalities during pravastatin therapy were not confirmed. Safety and tolerability are similar to placebo.

EXCEL

(Expanded Clinical Evaluation of Lovastatin)

- Randomized, double-blind, 8245 patients, lovastatin at various dosages and times (20mg with evening meal, 40 mg q evening, 20 mg bid morning and evening meal, and 40 mg bid, and placebo)
- The increase in receptor mediated removal of LDL from the plasma accounts for the large reductions in LDL cholesterol level achieved with lovastatin.
- This study treated patients with moderate hypercholesterolemia.
- 40% of patients had HTN, 92% white, 59% men, 29% had CHD, 30% overweight
- 47 patients had transaminase levels >3 times ULN. 32 had elevated ALT only and 14 had elevated ALT and AST levels, and one had elevated AST only
- The elevations in transaminase levels confirms the need to monitor patients during the first year of therapy
- Muscle symptoms with a CK level elevated >10 times the ULN were observed in 5 patients
- The most reported adverse effects were constipation, palpitations and insomnia
- Patients at higher risk may require larger doses of lovastatin and in some instances may require the addition of a second drug to reach LDL cholesterol levels recommended by the NCEP guidelines
- We concluded that Lovastatin, when added after an adequate trial of a prudent diet, is a highly effective and generally well-tolerated drug for the treatment of patients with moderate hypercholesterolemia

Variable	Placebo	20mg q pm	40mg q pm	20mg bid	40mg bid
LDL	+0.4	-24	-30	-34	-40
HDL	+2.0	+6.6	+7.2	+8.6	+9.5
Total	+0.7	-17	-22	-24	-29
Triglycerides	+3.6	-10	-14	-16	-19

MRC/BHF Heart Protection Study

- Simvastatin 40 mg, randomized, 20,536 patients (15,454 men and 5,082 women) with coronary disease, other occlusive diseases, or diabetes.

	Simvastatin	**Placebo**
Death	1328	1507
Coronary deaths	587	707
Other vascular causes of death	194	230
Non-fatal or fatal stroke	444	585
Non-fatal MI	898	1212
Non-vascular death	547	570
Myopathy (Rhabdomyolysis)	5	3
Any Cancer/GI Cancer (most common)	814/ 228	802/ 223

- The study states that five years of simvastatin would prevent about 70-100 people per 1000 from suffering from at least one of these major vascular events, and longer treatment should produce further benefit.
- Simvastatin produced a risk reduction of 25%
- The size of risk reduction produced by lowering LDL can be determined more by an individual's overall risk of cardiovascular disease rather than just their initial blood lipid concentration.
- There was no significant difference in the number of patients with elevated ALT 2-4 x ULN (139 vs. 131 placebo) or CK 4-10 x ULN (19 vs. 13 placebo).
- This trial suggests that there is no need for routine liver functional test when using this regimen or other statin regimens except to monitor patients with pre-existing liver disease.
- Patients with LDL below 100 mg/dL still benefited from a reduction in their LDL. Simvastatin safely reduced some patient's LDL to 65 mg/dL and produced as great of a reduction found in patients with higher risk.

Attaining United States and European Guideline LDL-cholesterol Levels with Simvastatin in Patients with Coronary Heart Disease

(the GOALLS Study)

Author(s): Fausto Garmendia; Alan S. Brown; Istvan Reiber; Philip C Adams
Source: Current Medical Research and Opinion; Volume: 16 Number 3 Page: 208-219

The effectiveness and safety of simvastatin in reducing low-density lipoprotein cholesterol (LDL-C) to target levels in patients with coronary heart disease (CHD) were evaluated in the GOALLS (Getting to Appropriate LDL-C Levels with Simvastatin) study. This multinational, multicentre, prospective, open-label, study consisted of a six-week diet washout period followed by a 14-week titrate-to-goal treatment period with simvastatin. 198 men and women with documented CHD and a fasting LDL-C level between 115 mg/dL (3.0mmol/l) and 180 mg/dl (4.7 mmol/l) and triclycerides (TGs) ≤ 400 mg/dL (4.5 mmol/l) were enrolled. The patients were started on 20 mg simvastatin with dose titration up to 80 mg if the LDL-C remained above 100 mg/dL at weeks 6 and 10. The key efficacy parameters were the percentage of patients achieving US and European LDL-C goals [≤ 100 mg/dL (2.6 mmol/l) and ≤ 115 mg/dL (3.0 mmol/l), respectively]. Safety was evaluated by monitoring laboratory tests and recording adverse events. After 14 weeks of simvastatin (20-80 mg) treatment, approximately 90% of the patients achieved LDL-C goals according to US (87%) and European (94%) guidelines. Most patients (72-93%) achieved target LDL-C levels on 20 mg simvastatin. An estimated 14% of the patients required titration to the 80 mg dose. Treatment with simvastatin (20-80) produced statistically significant improvements in all measured lipid variables by the end of the study. The mean reductions in total cholesterol and LDL-C, and the median reduction in TG, were 28%, 41% and 16%, respectively. The increase in high-density lipoprotein cholesterol and apolipoprotein A-1 were 5% and 4%, respectively. Simvastatin was well tolerated across the dosage range. In conclusion, simvastatin, 20-80 mg/day, was safe and highly effective at reducing LDL-C levels. The recommended US and European LDL-C treatment goals were achieved in approximately 90% of the patients. These goals were similarly achieved for a variety of high-risk sub-groups (hypertensives, diabetics and elderly patients).

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SSRI ANTIDEPRESSANTS REVISITED – PEDIATRIC CONSIDERATIONS

At the July 2, 2003 P&T Committee meeting, when addressing the issue of SSRI antidepressants to be considered for preferred drug status, the P&T Committee voted to amend the original recommendation that "no brand name SSRI antidepressant is recommended for preferred drug status." The amendment requested that sertraline (Zoloft) be accepted for preferred drug status in the pediatric (age 18 and under) population for the treatment of major depressive disorder (MDD).

Since the July 2 meeting, it has been determined that **fluoxetine** (Prozac) is the **only SSRI** antidepressant that has an **FDA-approved pediatric indication** to treat **MDD.** This indication is only for pediatric patients in the **8 to 18** year old age range at dosage levels specified in the package labeling.

Fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro) are FDA-approved to treat **MDD** in **adults**.

Three (3) SSRI antidepressants have pediatric indications for the management of obsessive-compulsive disorder (OCD). These are fluoxetine (Prozac) for ages 8 to 18, fluvoxamine (Luvox) for ages 8 to 17 and sertraline (Zoloft) for ages 6 to 17.

The SSRI "gold standard," fluoxetine, is available generically. There is no compelling evidence-based clinical justification for placing any brand name SSRI antidepressant in preferred drug status to treat pediatric depression (for which only fluoxetine is indicated) or for treating OCD (for which fluoxetine is indicated in the 8 to 18 year old population).

Further, British regulators have urged a halt to prescribing paroxetine (Paxil) in children and adolescents due to its apparent potential to increase suicidal thought and behavior. In a study published by GlaxoSmithKline, the manufacturer of Paxil, children between the ages of 7 and 18 receiving Paxil had a higher than normal incidence of mood swings, crying, suicidal thoughts and potential suicidal behavior. No suicides occurred during the study, however. The British government is examining the potential of Paxil to produce suicidal ideation in adults.

The U.S. Food and Drug Administration (FDA) was quick to issue warnings against on-label (e.g. OCD) and off-label (e.g. MDD) prescribing of Paxil in children. Guidelines for do's and don'ts regarding Paxil use are available on the FDA web-site at http://www.fda.gov/cder/drug/infopage/paxilQ&A.htm and at the Legal News Watch web-site at http://www.legalnewswatch.com/news_216.html .

There is no current evidence that Paxil-induced suicidal ideation is a "class effect" but SSRI-associated suicidal thought does suggest cautious use of any SSRI antidepressant in pediatric patients, particularly for off-label use.

Sertraline (Zoloft) continues to be evaluated in children and adolescents for the management of major depressive disorder. In the August 27, 2003 issue of the *Journal of*

the American Medical Association (JAMA), a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy, safety and tolerability of sertraline v. placebo in treating 6 to 17 year old patients with MDD was published. The study group (N=189) received doses of sertraline 50 to 200 mg per day and the placebo group (N=187) received a matching placebo tablet. Standard outcome measures were employed, and results indicated that sertraline is an effective and well-tolerated short-term treatment in 6 to 17 year old children and adolescents with MDD.

Although this study will obviously contribute to a potential FDA-approved indication for sertraline in the treatment of pediatric MDD, such use remains off-label. Unanswered questions regarding a "class effect" of suicidal ideation associated with SSRI use in pediatric patients remain to be answered.

In view of this clarification of FDA-approved pediatric indications of SSRI antidepressant use in pediatric patients who may be at increased risk for SSRI-induced suicidal thought and behavior, it is recommended that the P&T Committee rescind its recommendation that sertraline (Zoloft) be given preferred drug status for pediatric use (children 18 and younger) and that no brand name SSRI antidepressant be placed in preferred status.

SEDATIVE-HYPNOTICS REVISITED – GERIATRIC CONSIDERATIONS

At the August 6, 2003 P&T Committee meeting, when addressing the issue of sedative-hypnotics to be considered for preferred drug status, the P&T Committee voted to table, for further evaluation, the recommendation that "no brand name first generation benzodiazepine or nonbenzodiazepine GABA agonist is recommended for preferred drug status."

P&T Committee discussion revolved around the clinical propriety of benzodiazepine GABA agonist use in the elderly in the context of the "Beers List." The possible addition of a brand name nonbenzodiazepine GABA agonist to the recommendation for preferred status was discussed.

The Beer's List is a national guideline for fostering safe, appropriate and effective medication management in the elderly. Criteria were originally developed in 1991 (Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med*. 1991;151:1825-32). These criteria were updated in 1997 (Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. *Arch Intern Med*. 1997;157:1531-36.) and are included in Attachment A for review.

Table 1 of Attachment A (Beer's List) is a list of medications to avoid or use within specified dose and duration ranges in elderly patients. These criteria were developed specifically for the frail elderly patient, especially those who are residents of long-term care facilities. The drugs in Table 1 do not represent absolute contraindications, are not absolutely contraindicated in the elderly as per the package labeling, and may be acceptable for use in most elderly patients.

Table 2 of Attachment A (Beer's List) is a suggested list of medications to avoid in elderly patients with specific diseases. Risk severity is rated as low or high. Medications suggested for avoidance in the elderly under certain medical conditions are not in alignment with package labeling as they are not typically listed as absolute contraindications in package labeling. The drug-disease recommendations in Table 2 of the Beer's List (attachment A) are typically presented as warnings, precautions, risk factors, or special considerations for special populations in the package labeling. Selection and use is then left to the clinical judgment of the prescriber.

Within the specific context of sedative-hypnotic prescription drugs, the potential problem/relative risk is listed as the same between the benzodiazepine GABA agonists, temazepam and triazolam, and the nonbenzodiazepine GABA agonist, zolpidem (Table 1, Attachment A). Guidance in the Beer's List is on selecting appropriate doses of temazepam (15 mg), triazolam (0.25 mg) or zolpidem (5 mg). The Beer's List ranks the potential severity of risk from use of temazepam, triazolam and zolpidem as low for all three agents.

In Table 2 of the Beer's List (Attachment A), which addresses suggestions for medications to avoid in elderly patients with specific concomitant diseases, the sedative-hypnotics as a class are listed as drugs that represent high risk in patients with chronic obstructive pulmonary disease The Beer's List does not recognize nonbenzodiazepines as a safer or more appropriate sedative-hypnotic than benzodiazepines regardless of duration of action, active metabolites v. no active metabolites and so forth.

In Table 2 of the Beer's List (Attachment A), the long-acting benzodiazepines are suggested as medications to avoid in elderly patients with vascular disorders that predispose them to syncope and falls. The benzodiazepine GABA agonists, temazepam and triazolam, are not long-acting benzodiazepines. Temazepam is intermediate in its duration of action and triazolam is short-acting. The Beers List does not address or differentiate risk between temazepam, triazolam or zolpidem in elderly patients with vascular disorders.

RECOMMENDATION

The previous sedative-hypnotic review, review of available clinical studies, and assessment of the updated Beer's List (1997) does not present clinical evidence sufficient to support the recommendation of any brand name nonbenzodiazepine or benzodiazepine GABA agonist over multisource triazolam or temazepam on grounds of greater efficacy, safety or tolerability. Specifically, the nonbenzodiazepine GABA agonists, zaleplon and zolpidem, show no significant clinical advantage over multisource triazolam or temazepam relative to efficacy, safety and tolerability.

No brand name sedative-hypnotic agents are recommended to the P&T Committee for preferred drug status.

Attachment A

Beer's List

Table 1.

Table 2.